page 1, lines 9-13, which indicates that OmpC is the bacterial antigen "outer membrane protein C." No new matter has been added by this amendment.

Attached hereto as Appendix A is a marked up version of the amended claims showing specific text changes made in the enclosed amendment using underlining to indicate added text.

Regarding the Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 to 7 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed.

The Office Action indicates that claims 1 and 2 are allegedly indefinite in reciting "OmpC" because an acronym or abbreviation must be recited at least one time in a set of claims. Applicants submit that there is no requirement in 35 U.S.C. § 112, second paragraph, for the definition of an abbreviation or acronym to appear in the claims. Rather, definiteness of claim language must be analyzed in light of the disclosure in the application, teachings of the art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (M.P.E.P. § 2173.02).

In this case, the specification clearly indicates that "OmpC" is the abbreviation for outer membrane protein C (see, for

example, page 1, lines 9-13, and page 6, lines 2-4). The term "OmpC" also is well known in the art, as evidenced, for example, by U.S. Patent No. 6, 033,864 to Braun et al. (see column 11, lines 50-52). Thus, Applicants submit that one of skill in the art in view of the specification and general knowledge in the art would know that "OmpC" refers to "outer membrane protein C." Nevertheless, to advance prosecution, Applicants have amended claims 1 and 2 to recite "outer membrane protein C" the first time "OmpC" is recited. Since the terms "outer membrane protein C" and "OmpC" are equivalent, the amendment to claims 1 and 2 does not alter the scope of the amended claims.

Claim 2 also is rejected under the second paragraph of 35 U.S.C. § 112 as allegedly incomplete for omitting essential elements. In particular, the Office Action indicates that it is unclear how the detection step is effected in the absence of a label.

Applicants submit that claim 2 is clear as written and that the recited detection step can be performed with or without a label. Specifically, detection of the IgA anti-OmpC antibody can be performed directly, for example, through labeling of the antibody itself or detection can be performed indirectly, for example, using a secondary antibody such as an enzyme-linked secondary antibody. It is understood that the claim as written encompasses these and other conventional means of detection. Thus, the claim is clear and complete as written, and the Examiner is respectfully requested to remove this ground for

rejecting claim 2 under the second paragraph of § 112, second paragraph.

The Office Action also indicates that claim 3 is indefinite due to the term "substantially". In this regard, it is alleged that the term is not defined by the claim, that the specification does not provide a standard for ascertaining the requisite degree, and that one of skill in the art would not be reasonably apprised of the scope of the invention.

Claim 3 is directed to the diagnostic method of claim 2 in which the recited OmpC antigen has substantially the amino acid sequence of SEQ ID NO: 1. Applicants respectfully submit that one of skill in the art would be reasonably apprised of the scope of the invention based upon the disclosure in the specification. In particular, the specification teaches that an OmpC antigen is a protein that has linear or conformational homology to OmpC and further teaches that an OmpC antigen has at least 50% amino acid identity with *E. coli* OmpC (SEQ ID NO: 1; page 9, lines 5-16). In regard to the I-2 polypeptide, the specification discloses that a polypeptide having "substantially the same amino acid sequence as SEQ ID NO: 3" can be a naturally occurring polypeptide or a related polypeptide having substantial amino acid sequence similarity to the naturally occurring sequence, for example, an isotype variant or homolog of SEQ ID NO: 3 (see page 20, lines 18-24). Thus, in view of the specification, one of skill in the art readily recognizes that the phrase "substantially the amino acid sequence of SEQ ID NO: 1" means an OmpC antigen having the amino acid sequence SEQ ID

NO: 1 or an isotype variant or homolog of SEQ ID NO: 1 or another related polypeptide having substantial amino acid similarity to SEQ ID NO: 1. Because the claim is clear and definite to the skilled person, Applicants respectfully request that the Examiner reconsider and remove this ground for rejecting claim 3 under 35 U.S.C. § 112, second paragraph.

Having addressed each of the grounds for rejecting the claims as allegedly indefinite, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 7 under 35 U.S.C. § 112, second paragraph.

Regarding the rejection of claims 1 to 4 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,033,864 to Braun et al.

The rejection of claims 1 to 4 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,033,864 to Braun et al. is respectfully traversed. The Office Action asserts that Braun et al. report that bacteria have been implicated in the initiation and progression of Crohn's disease, that the porin antigen is expressed by bacteria of ulcerative colitis and Crohn's disease patients, and that Braun et al. describe a method of diagnosing Crohn's disease by detecting anti-OmpC antibodies. Applicants respectfully disagree with these assertions for the reasons set forth below.

Applicants would respectfully remind the Examiner that, to anticipate a claim, a reference must teach each and every

element of the claim (Verdegeal Bros. v. Union Oil Co. of California, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987); Richardson v. Suzuki Motor Co., 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989)). The present claims relate to the diagnosis of Crohn's disease and require, in part, detecting the presence or absence of IgA anti-OmpC antibodies.

As noted in the Office Action, Braun et al. indicate that bacteria have been implicated in the initiation or progression of Crohn's disease (CD) as supported, for example, by the efficacy of antibiotics and diet in mitigating disease in some Crohn's disease patients (column 1, lines 60-65). It is Applicants' position that such a general and speculative statement that bacteria may play a role in Crohn's disease is insufficient to support a rejection based upon anticipation, because it does not provide a teaching of each and every element of the claims. Specifically, such a statement does not teach determining the presence or absence of IgA anti-OmpC antibodies.

Furthermore, the cited patent by Braun et al. describes diagnosis of ulcerative colitis (UC) by detection of a pANCA-reactive porin antigen having linear or conformational homology to OmpF, OmpC, or another *E. coli* porin (column 2, lines 22-31; column 12, lines 1-3). However, contrary to the Office's assertion, Braun et al. do not teach diagnosis of Crohn's disease by detection of IgA anti-OmpC antibodies. Rather, Braun et al. describe the use of pANCA-reactive proteins to diagnose ulcerative colitis, a disorder which is distinct from Crohn's disease. See, for example, column 5, lines 10-18; and column 11,

lines 8-24, which each describe methods of diagnosing ulcerative colitis with a pANCA-reactive antigen. See, also, the cited patent at column 10, line 55, to column 11, line 10, which indicates that

> The present invention also relates to a UC pANCA protein antigen expressed by enteric bacteria of UC patients.... These results indicate that microbial antigens lacking detectable linear sequence homology to histone H1 can be expressed by enteric colonic bacteria in UC patients and can play a role in the immune dysregulation in UC. Isolation of the porin antigen disclosed herein provides a novel UC pANCA target antigen for diagnosing and treating ulcerative colitis. (emphasis added)

Nowhere does the cited patent by Braun et al. teach diagnosis of Crohn's disease by detecting the presence or absence of IgA anti-OmpC antibodies. In sum, while the cited patent reports the use of pANCA-reactive porin antigens for diagnosis of ulcerative colitis, it does not teach methods of diagnosing Crohn's disease, which is a distinct disorder. Thus, Braun et al. does not teach each and every element of the claims and cannot anticipate the claimed invention.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 1 to 4 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,033,864 to Braun et al.

Regarding the rejection of claims 5 to 7 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,033,864 to Braun et al. in view of U.S. Patent No. 5,932,429 to Targan et al.

The rejection of claims 5 to 7 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,033,864 to Braun et al. in view of U.S. Patent No. 5,932,429 to Targan et al. is respectfully traversed.

Claims 5 to 7 are drawn to a method of diagnosing Crohn's disease in a subject by detecting the presence or absence of IgA anti-OmpC antibodies in the subject and further determining the presence or absence of IgA *anti-Saccharomyces cerevisiae* antibodies (ASCA) in the subject, where the presence of either IgA anti-OmpC antibodies or ASCA independently indicates that the subject has Crohn's disease.

Claims 5 to 7 rely, in part, on detecting the presence or absence of IgA anti-OmpC antibodies. As noted above in regard to the rejection of claims 1 to 4 under 35 U.S.C. § 102(e), the cited patent by Braun et al. fails to teach a method for diagnosing Crohn's disease by detecting IgA anti-OmpC antibodies. Rather, Braun et al. describe a method for diagnosing a distinct disorder, ulcerative colitis, by detecting a UC pANCA target antigen (column 11, lines 7-13). Furthermore, Braun et al. teach away from the invention by reporting that OmpC is reactive with pANCA antibodies, which are known in the art to be associated with ulcerative colitis. In this regard, see Braun et al. at column 1, lines 52-55, which indicates that autoantibodies

against cytoplasmic components of neutrophils (pANCA) have been reported in 68-80% of patients with ulcerative coliti (see, also, column 4, lines 41-45). Braun et al. further report that Western analysis demonstrated that OmpC was specifically reactive with the UC pANCA monoclonal antibody, NANUC-2 (column 10, lines 55-66). See, also, column 26, lines 46-49, which indicates that NANUC-2 is a representative UC pANCA monoclonal antibody isolated from a phage display library. In view of the fact that pANCA antibodies were known in the art to be generally elevated in UC patients, pANCA antibody reactivity to OmpC teaches away from the claimed invention by leading one skilled in the art to use this antigen for diagnosis of ulcerative colitis rather than Crohn's disease. Thus, the claimed invention is unobvious over Braun et al., which teaches away from the claimed invention.

Nothing in Targan et al. overcomes the deficiency of Braun et al. Firstly, Targan et al. do not describe a method of diagnosing Crohn's disease. Rather, Targan et al. report diagnosis of a clinical subtype of Crohn's disease that exhibits characteristics of ulcerative colitis in a patient already known to have Crohn's disease (column 3, lines 1-5). Secondly, the methods of Targan et al. rely on assaying for the presence or absence of perinuclear anti-neutrophil cytoplasmic antibody ("pANCA"), which is by definition a "neutrophil" antigen (column 7, lines 17-21) and assaying for the presence or absence of ASCA (column 12, line 63, to column 13, line 8). However, Targan et al. do not teach or suggest using OmpC, which is a microbial antigen, to detect the presence or absence of IgA

anti-OmpC antibodies for diagnosis of Crohn's disease and, thus, cannot supply what is missing in the primary reference.

In sum, neither of the cited patents to Braun et al. or Targan et al., alone or in combination, teach or suggest the claimed methods of diagnosing Crohn's disease, which rely, in part, on detecting the presence or absence of IgA anti-OmpC antibodies. Accordingly, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 5 to 7 under 35 U.S.C. § 103.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney or Cathryn Campbell.

Respectfully submitted,

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APPENDIX A

Amendments to claims:

1. (Amended) A method of diagnosing Crohn's disease in a subject, comprising determining the presence or absence of IgA anti-outer membrane protein C (anti-OmpC) antibodies in said subject,

where the presence of said IgA anti-OmpC antibodies indicates that said subject has Crohn's disease.

2. (Amended) A method of diagnosing Crohn's disease in a subject, comprising the steps of:

(a) obtaining a sample from a subject suspected of having inflammatory bowel disease;

(b) contacting the sample with an outer membrane protein C (OmpC) antigen, or reactive fragment thereof, under conditions suitable to form a complex of the OmpC antigen, or reactive fragment thereof, and IgA antibody to the OmpC antigen;

(c) contacting said complex with an anti-IgA antibody; and

(d) detecting the presence or absence of IgA anti-OmpC antibodies,

where the presence of said IgA anti-OmpC antibodies in said subject indicates that said subject has Crohn's disease.